# Rabies pre-exposure prophylaxis schedules and serological monitoring of high-risk exposure populations

**Jesse Blanton, DrPH**

Epidemiologist

Advisory Committee on Immunization Practices

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National Center for Emerging and Zoonotic Infectious Diseases

Division of High-Consequence Pathogens and Pathology

# Overview

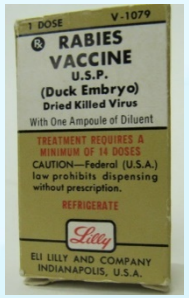
- Question for consideration
- Historical perspective of Pre-exposure prophylaxis schedules
- Vaccine potency and immunogenicity
- Routes of administration
- Review of evaluated PrEP schedules
- Boosters and duration of immunogenicity
- Special Populations

# For your consideration…

- **Status quo**
  - 3-dose, 3-4 week schedule [0,7, 21 or 28]
  - Serological monitoring and boosters based on risk category

- **Should a 2-dose, 1-week schedule [0,7] for rabies PrEP be recommended?**
  - Recommended routes of administration
  - Special populations
    - High risk categories: booster/serological monitoring?
    - Immunocompromised: alternate schedules/serological monitoring?
  - All rabies vaccines are FDA approved as 3-dose series for PrEP

# Rabies PrEP Recommendations


Nerve Tissue Vaccines

Duck Embryo Vaccine

Cell Culture Vaccines (e.g. HDCV, PCEC)

1885: Pasteur develops rabies Vaccine

1967: [0, 28] + [196] SQ
or
[0, 7, 14] + [98] SQ

1980: [0, 7, 21/28] IM

1984: [0, 7, 21/28] IM/ID

2008: [0, 7, 21/28] IM

2018: WHO [0, 7] IM/ID
or
[0] + [w/in 1 year]

*Timeline not to scale

# Vaccine Potency

- Modern rabies vaccine highly potent
- WHO and ACIP recommend ≥2.5 IU potency
- Potency and immune response correlated up to 2.5IU / IM dose
  - No significant association identified above 2.5IU (or 0.5IU / dose ID)

IM

Table 3 **Assessing the relationship between vaccine potency and immune response**

| Day | Vaccines | No. of subjects | GMT | GSD | Immune response (RVNA Titers) in the vaccinees | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SE (GMT) | GMR | 95% CI for GMR | | t-value* | df | p-value (2-tailed) |
| 14 | Lower potency (≥2.5 and <5 IU) | 161 | 5.55 | 3.32 | 1.10 | 1.06 | 0.82 | 1.37 | 0.42 | 409 | >0.66 |
| | Higher potency (≥ 5 IU) | 250 | 5.25 | 3.95 | 1.09 | | | | | | |

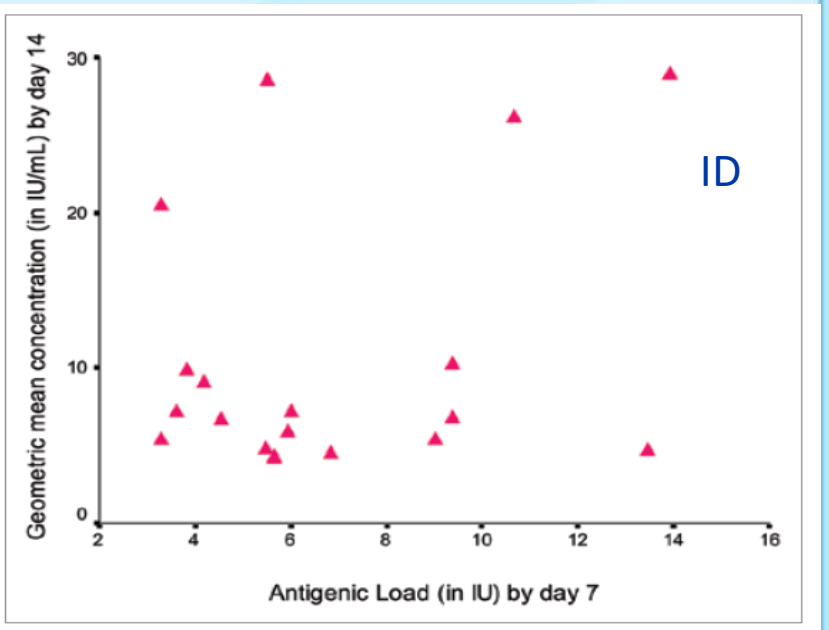
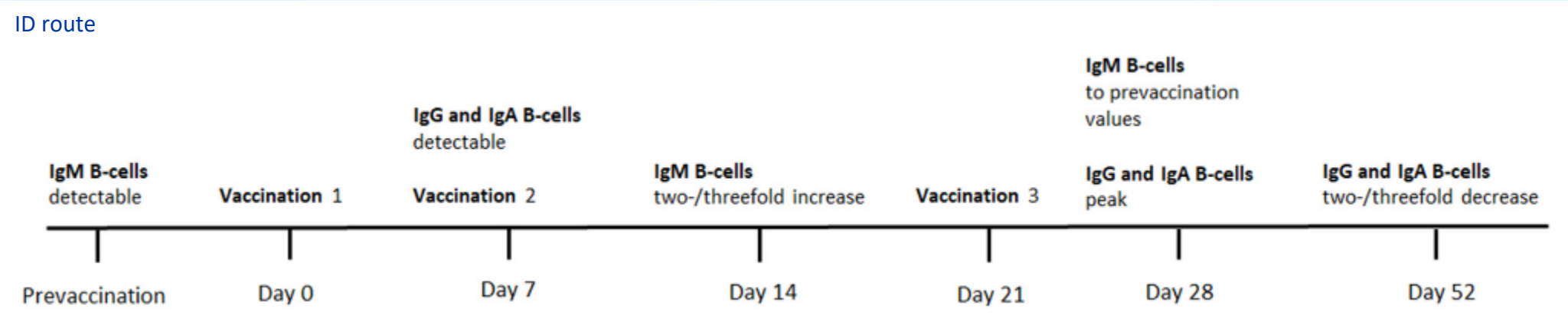



**Figure 1.** Correlation between antigenic load by day 7 versus GMC by day 14 ($r = 0.289$, $p > 0.230$).

Sudarshan et al. (2005 and 2010). Hum Vaccin.

# Kinetics of Rabies Vaccine Immune Response

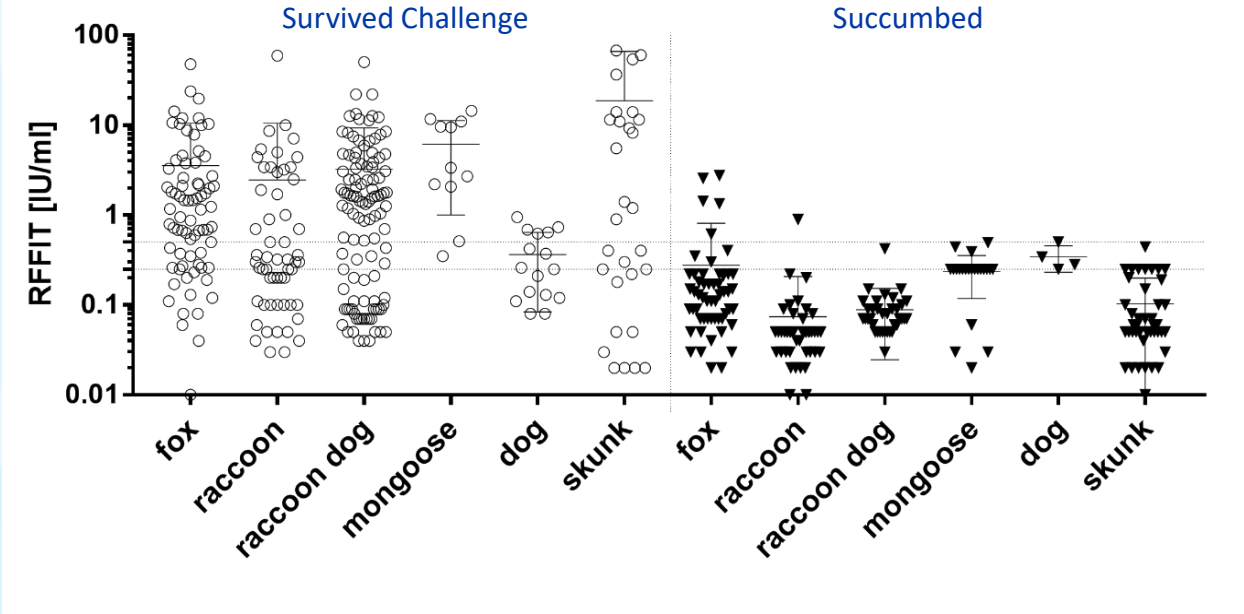


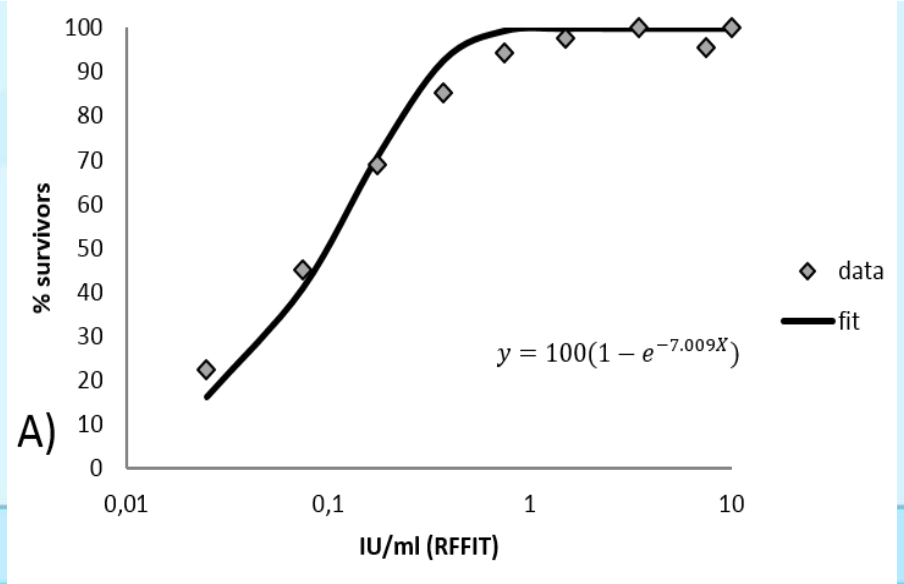

- **Limited Studies beyond neutralizing antibody response**

Overduin et al. (2019) Vaccine

# Neutralizing Antibody as Surrogate of Protection

- 0.5 IU/mL rabies neutralizing antibodies (RFFIT)
  - Not a measure of protection
  - Measure of adequate response
  - Reliable detection limit
- Correlation between antibody titer and survival
- Variability between species
- Adequate antibody response after primary vaccination and anamnestic response to challenge best surrogates



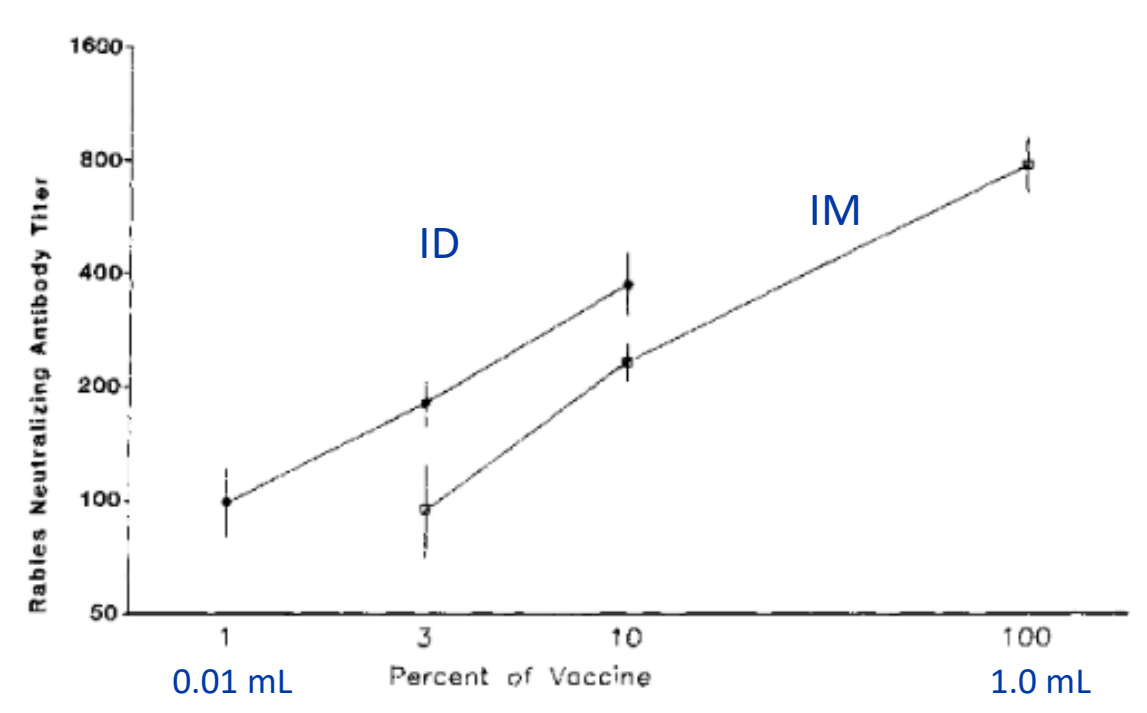

Rabies Virus Antibodies from Oral Vaccination as Correlate of Protection against Lethal Infection in Wildlife

Moore S, et al. (2017). Trop Med Infect Dis.,

# Vaccination Route

- ID globally recommended vaccination route since 1980s
  - ACIP recommendation 1984-2008
- ID found more cost effective in most settings and dose sparing in supply limited settings

- No licensed single use ID packaging or multi-draw vials for rabies vaccine
- Injection safety not well studied in setting of rabies ID administration
- Cost effectiveness (ID v IM) relational to PrEP or PEP patient volume




Fishbein et al. (1987). JID, Hampson et al. (2011). PLoS NTD.

# Pre-exposure Prophylaxis (PrEP) Schedules

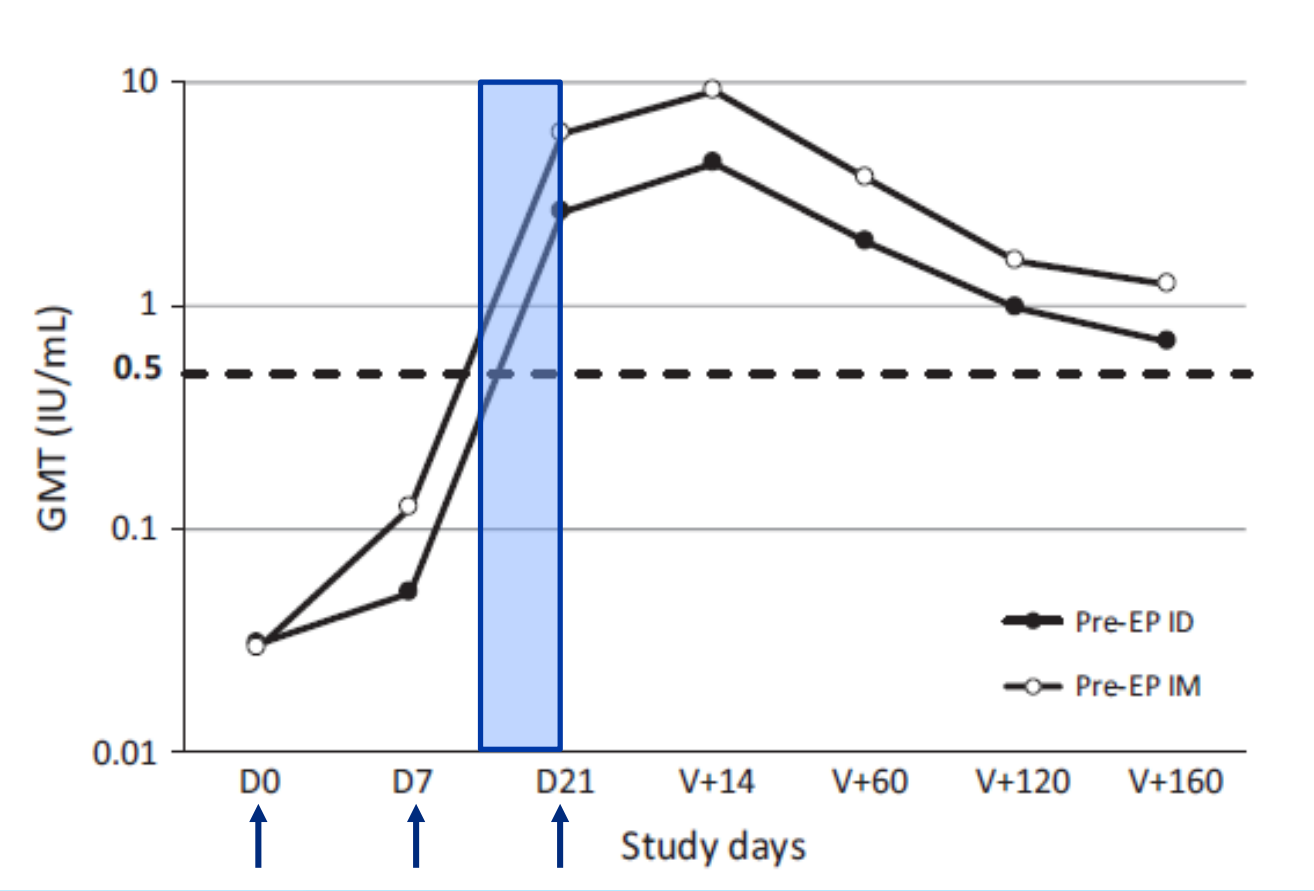
- **3-dose**
  - 0, 7, 21/28*
  - 0, 3, 7
- **2-dose**
  - 0, 28
  - 0, 7**
- **1-dose**
- **Childhood immunization schedules (typically 2-dose, 2-3 months apart)**
- **Most schedules evaluated by both IM and ID routes**

*Current ACIP recommended schedule

**Recently recommended WHO schedule

# 2-dose, 1-week Schedule

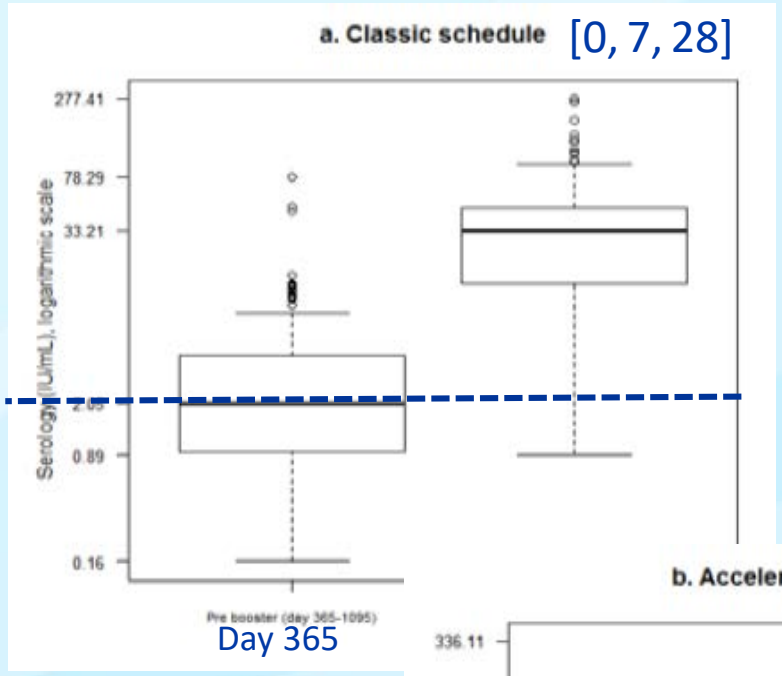
- **2018: Recommended WHO PrEP Schedule (IM or ID)**
- **1 dose vaccine administered IM on days 0 and 7**
- **Primary response well documented**
  - Infer from existing 3-dose schedule

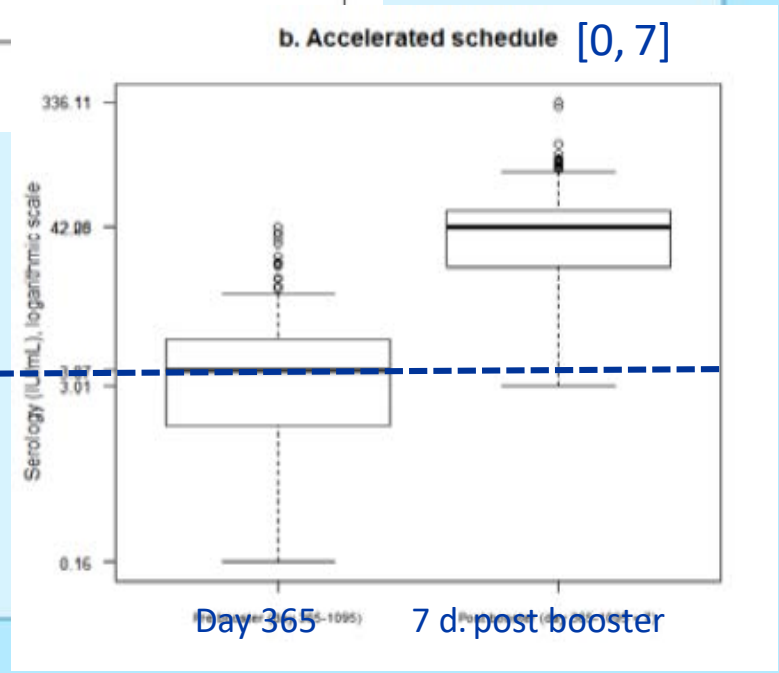



Recuenco et al. (2017) Vaccine

# 2-dose, 1-week Schedule

- **Clinical Trials**
  - ID
  - N=500
  - 100% adequate response at day 35
  - 2-dose group had significantly higher GMT at 1 year compared to 3-dose
  - No difference in post-booster response at 1 year



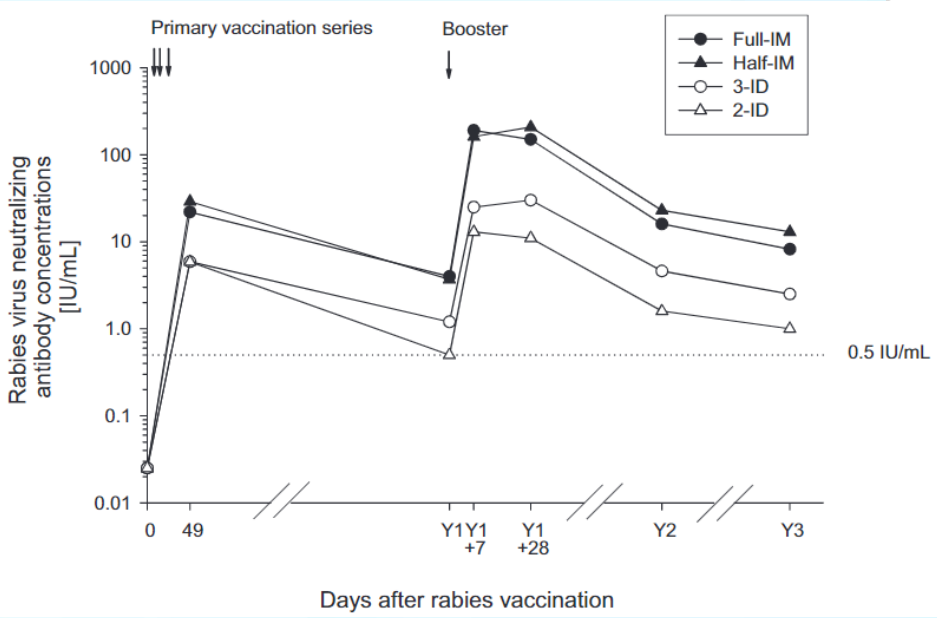

Soentjens et al. (2018) CID.

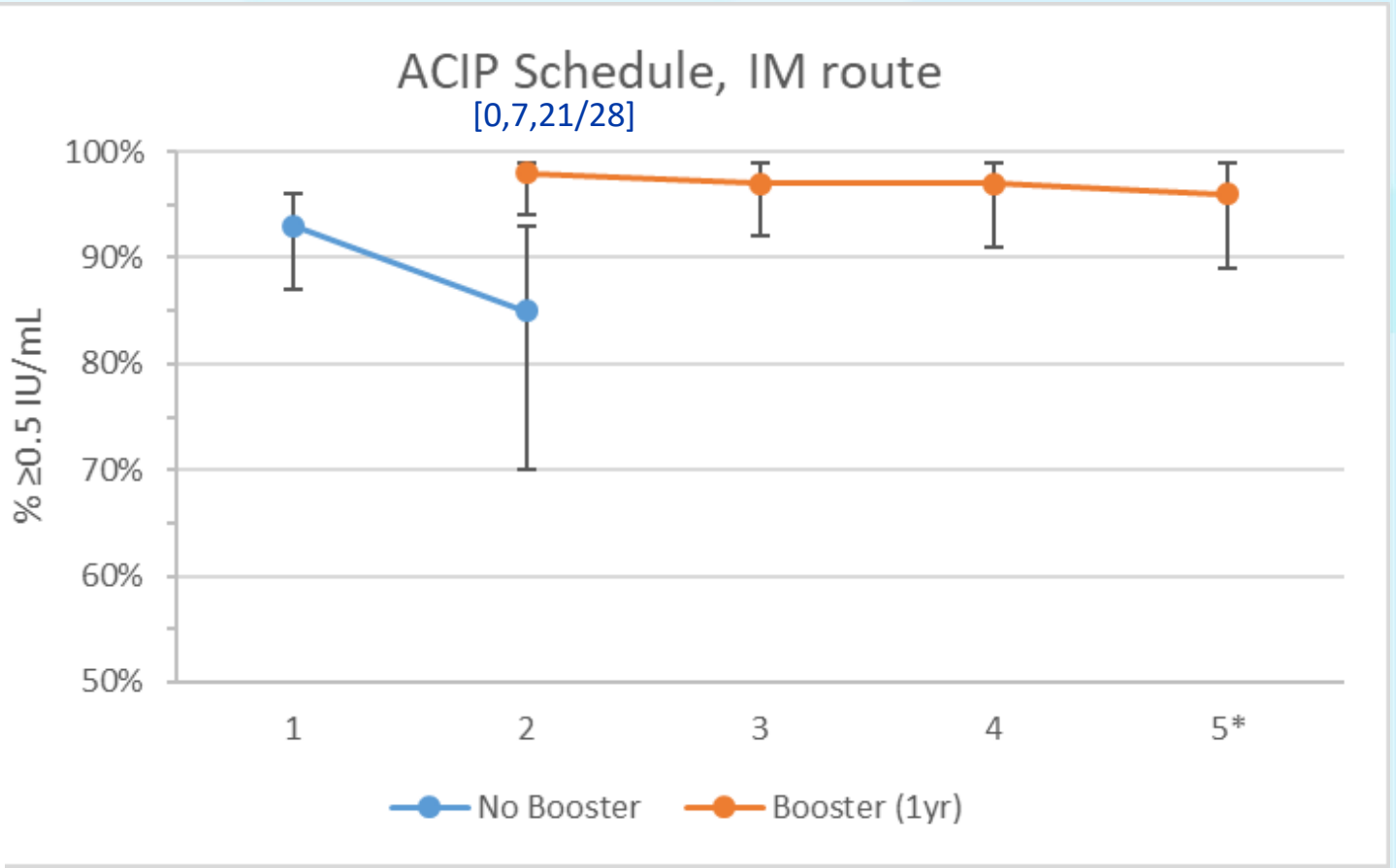
# Duration of Immunogenicity - Evidence

- **Follow-up typically less than 1 year**
- **Longer follow-up**
  - Mostly [0, 7, 21/28] schedules
  - Few [0, 28]
- **Primary response titer not effective at predicting duration of immunogenicity**
  - Titer at 1 year or post booster significantly associated with titer 2-7 years later
  - Titers >30 IU/mL post 1 year booster associated with adequate response 5-10 years later

# Booster

- **Booster at 1 year associated with long term immunogenicity**

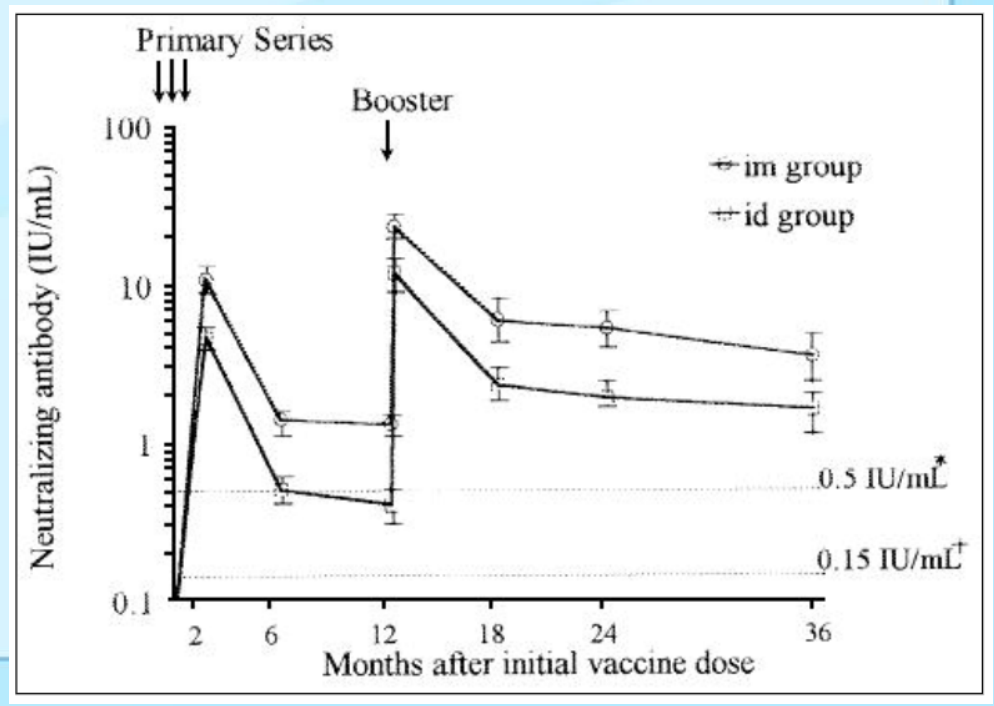



Pengsaa et al (2009) Ped Infect Dis Jrnl

# Booster Response

- **Anamnestic response nearly universal to vaccine booster**
  - One non-responder reported in study (later diagnosed with B-cell Lymphoma)
- **Survival following exposure w/o booster**
  - 2010 Liver recipient from rabid donor in Germany
    - Vaccinated >20 years prior, anamnestic response documented
  - Reports of significant titer increases following bat bites among wildlife biologist
  - Reduction in rabies cases in Amazonia region of Peru after mass childhood immunization campaign




Sabchareon et al. (1998) Ped Inf Dis Journal, Maier et al (2010) CID,

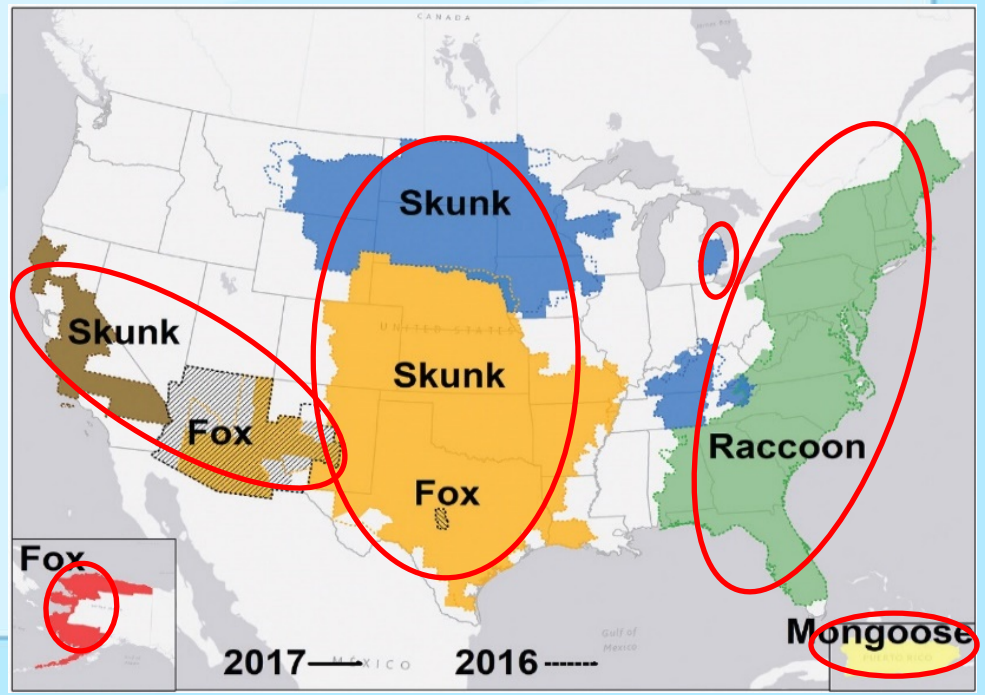
# PrEP Failure

- **1 well documented PrEP failure reported**
  - 1982, Peace Corp Volunteer, Vaccinated ID with HDCV vaccine in Kenya
    - Bitten by dog ~6 months later
    - Died of rabies 3 months after bite
  - Classically attributed to co-administration of chloroquine during PrEP series
    - Study at time found other groups give ID HDCV abroad at time had lower or undetectable titers compared to those in the US
    - Likely multiple causes
- **Inadequate response to primary vaccination reported in immunocompromised persons**

Bernard et al. (1985) AJTMH

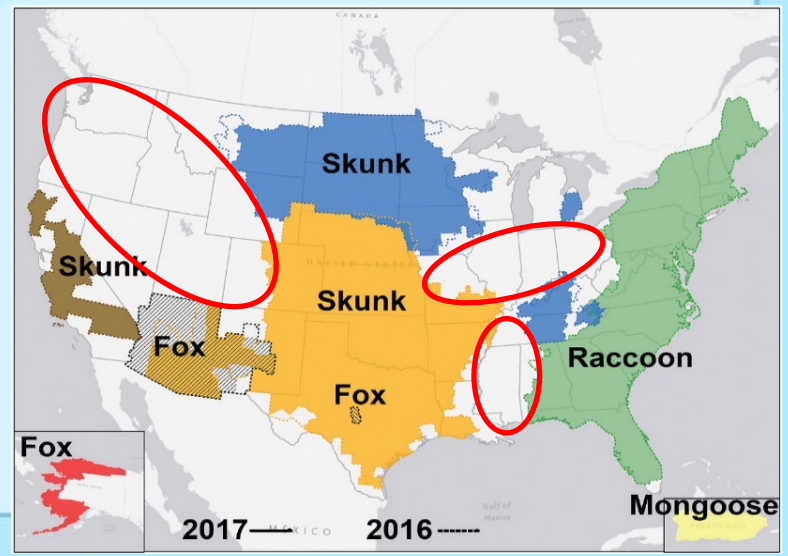
# Special Populations – High Risk

- **High risk (Continuous and Frequent) categories**
  - High rate of exposure events, high risk of rabies from exposure
  - High titer (>0.5 IU/mL)
    - Unrecognized exposure or risk under underappreciated
    - Higher titer correlated with protection
  - Booster at 6-12 months after primary vaccination improve likelihood of maintaining adequate titer
    - Reduce frequency of serological monitoring



# Special Populations – High Risk

- **Moderate risk (Infrequent) category**
  - High rate of exposure events, low risk of rabies from exposure
  - Increased risk sporadic and shortly after primary vaccination (e.g. travelers)
    - Often limited time to complete vaccination series
  - Routine booster at 6-12 months and routine serological monitoring not critical
  - Adequate anamnestic response expected regardless of titer
  - Serology or booster if risk status changes



# Special Populations - Immunocompromised

- **Data scarce for any schedule**
- **Risk reduction**
  - Increased focus on exposure avoidance, appropriate PPE, and prompt health seeking behavior
- **Serological confirmation of adequate immune response recommended**
  - >0.5 IU/mL

# Special Populations – Pregnant Women

- **No safety concerns reported**
  - Scarce data
- **Risk reduction**
  - Increased focus on exposure avoidance, appropriate PPE, and prompt health seeking behavior
  - May consider deferring where risk reduction possible and PEP readily available

# Working Group Plans

- **February 2020 ACIP meeting**
  - Systematic review presentation
  - GRADE for 2-dose PrEP schedule

- **Future ACIP meetings**
  - Vote on PrEP schedule
  - Additional data for consideration of alternate PEP Schedule

# Thank you!

**For more information please contact Centers for Disease Control and Prevention**

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov